UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,309	08/20/2001	Gregory M. Fahy	FAH02 P-300A	7331

277 7590 10/29/2004

PRICE HENEVELD COOPER DEWITT & LITTON, LLP
695 KENMOOR, S.E.
P O BOX 2567
GRAND RAPIDS, MI 49501

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/933,309
Filing Date: August 20, 2001
Appellant(s): FAHY, GREGORY M.

MAILED
OCT 2 9 2004
GROUP 1600

Gunther J. Evanina
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 16 July 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct. Of course, the Examiner disagrees with the conclusion drawn by Appellant, for reasons of record.

(6) Issues

The Appellant's statement of the issues is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Greenstein *et al.*, 1987, J. Endocr. 112:345-350 (reference submitted by Appellant).

McCormick *et al.*, 1991, Aging:Immunology and Infectious Disease 3:19-26 (reference submitted by Appellant).

Goff *et al.*, 1987, Clin. Exp. Immunol. 68:580-587 (reference submitted by Appellant).

Perico *et al.*, 1991, J. American Soc. Neph. 2:1063-1071 (reference submitted by Appellant).

Odorico *et al.*, 1993, Transplantation 55:1104-1107 (reference submitted by Appellant).

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112, Second Paragraph

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

Claim 16 is drawn to a method for transplanting organs and grafting tissue into a patient comprising steps of: restoring immune system function by regenerating the patient's involuted thymus; injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus (or, in the case of bone marrow cell, peripherally); and then transplanting said organ or grafting said tissue.

Claim 16 is indefinite because the method comprises regenerating the patient's involuted thymus, but the steps of regenerating the involuted thymus have not been taught. The involuted thymus must be regenerated before the next step of injecting the immunological equivalent of the tissue or organ to be transplanted occurs. The claim does not set forth any steps involved in the method/process of regenerating an involuted thymus. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 16 is also indefinite because the term "immunological equivalent" is a relative term which renders the claim indefinite. The term "immunological equivalent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 16-22, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim is drawn to a method for transplanting organs and grafting tissue into a patient comprising steps of: restoring immune system function by regenerating the patient's involuted thymus; injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus (or, in the case of bone marrow cell, peripherally); and then transplanting said organ or grafting said tissue.

Greenstein *et al.* (J. Endocr. 1987, reference submitted by Appellant) teach that regeneration of an age-involuted thymus can be accomplished in rats using an analogue of luteinizing hormone-releasing hormone (LHRH). The LHRH analogue, however, also reduced testosterone concentrations to levels measured in orchidectomized (surgical removal of the testis) rats.

McCormick *et al.* (Aging:Immunology and Infectious Disease, 1991, reference submitted by Appellant) teach that regeneration of an age-involuted thymus can be accomplished in rats using growth hormone (GH). However, there was no significant improvement of cellular immune function and most importantly, there was a high incidence of hepatic tumors noted in the growth hormone treated mice.

Goff *et al.* (Clin. Exp. Immunol., 1987, reference submitted by Appellant)

discloses the dubious nature of discerning a regenerated thymus. Goff states, "a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function: immunological or endocrine function must also be assessed" (page 585, 3rd paragraph).

Perico *et al.* (J. American Soc. Neph., 1991, reference submitted by Appellant) does not conclusively demonstrate that immunosuppressive drugs do not interfere with the functional properties of the thymus. It has been shown that cyclosporin (CsA) and steroids used to inhibit T cell activation and to deplete them from peripheral circulation also induce changes in the structure and function of the thymus, which include a decrease in thymus epithelial and cortical cells. Perico states, "All of these experiments do not yet allow conclusions to be made on whether the theoretical possibility of achieving donor-specific tolerance to allografts would possibly apply to human transplantations". "One can not exclude the possibility that the mechanism we and others have described only applies to the peculiar immune system of rats" (page 1069, last paragraph).

Odorico *et al.* (Transplantation, 1993, reference submitted by Appellant) teach that the efficacy of tolerance induction by the intrathymic injection of donor spleen cells appears to depend on the concurrent administration of antilymphocyte serum (ALS) in rats. Omission of ALS from the preparative regimen or substitution of CsA (a non-T-cell depleting immunosuppressant) for ALS, abrogated the ability of an intrathymic splenocyte injection to promote unresponsiveness to cardiac allografts, suggesting that a transient depletion of mature peripheral T cells is required for tolerance induction by

this method.

While the literature submitted by Appellant teaches regeneration of age-involuted thymus, the experiments were only executed in rats, there was no significant improvement of cellular immune function and there were harmful side effects (reduced testosterone concentrations, hepatic tumors). The literature of record teaches an art, which reports the incidence of harmful side effects and is unpredictable regarding improvement of cellular immune function. Harmful side effects can affect a patient's immune system function, which is important for the claimed method.

The instant specification fails to teach how a patient can have an involuted thymus regenerated, then undergo an intrathymic injection and then an organ transplant or tissue graft. The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure. The instant specification only teaches the administration of arginine and DHEA and human growth hormone and DHEA. The specification does not provide guidelines to determine thymic atrophy or involution. The specification fails to teach how a thymus can be regenerated upon administration of human growth hormone and DHEA or human growth hormone and chromium picolinate in a patient. Claim 16 is a single means claim with respect to step 1.

The disclosure does not provide immunological or endocrine assays or employ experiments such as magnetic resonance imaging or morphology studies, which would discern that a thymus has been regenerated. The specification provides no guidance or working examples for intrathymic injection. The specification fails to teach or disclose working examples for transplanting an organ or grafting of tissue. The specification does

not consider factors such as rejection, age-related thymic involution versus other types of thymic involution, the side effects of immunosuppressants, ALS versus CsA, the high incidence of tumors and other side effects associated with GH. "Immunological equivalent of the tissue or organ to be transplanted" is not defined and the specification does not teach how to make such.

Most importantly, the instant invention involves the combination of techniques comprising restoring immune system function by regenerating the patient's involuted thymus; injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus (or, in the case of bone marrow cell, peripherally); and transplanting said organ or grafting said tissue. Neither the specification nor the literature of record teach the enablement of the instant invention. For the reasons discussed above, such experimentation would be undue for one skilled in this art at the time the invention was made.

Due to the large quantity of experimentation necessary to regenerate an involuted thymus, administer an intrathymic injection and transplant an organ or tissue, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of intrathymic injections and organ/graft transplants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(11) Response to Argument

A. Claim Rejections Under 35 U.S.C. 112, Second Paragraph

At the bottom of page 3 of the Brief, Appellant states that the Examiner correctly recited and/or characterized the subject matter of claim 16. At the beginning of page 4, Appellant summarizes the Examiner's 112, second paragraph rejection of claim 16. Appellant argues that the statement that the claim is drawn to regenerating the patient's involuted thymus is incorrect and that the Examiner's incorrect characterization of the claim may have led to an erroneous conclusion that claim 16 is indefinite. Appellant argues that there is nothing indefinite about injecting the immunological equivalent of the tissue or organ to be transplanted into a thymus that has been regenerated. Appellant maintains that the fact that the thymus has already been regenerated before the immunological equivalent material is injected into the thymus is expressly required by the claim. Applicant argues that the first step is restoring immune system function by regenerating the patient's involuted thymus. Appellant states that it is unclear what the Examiner is attempting to say by stating that the steps of regenerating the involuted thymus have not been taught. Appellant argues that whether the steps of regenerating the involuted thymus have or have not been taught is not relevant to a rejection under 35 U.S.C. 112, second paragraph. At the beginning of page 5 of the Brief, Appellant states that claim 16 is directed to a method for transplanting organs and grafting tissue into a patient, not a process for regenerating an involuted thymus. Appellant maintains that claim 16 recites active, positive steps, delimiting how the claimed method for transplanting organs and grafting tissue into a patient is actually practiced. Appellant

recites the steps in claim 16.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The Examiner understands that "a method for transplanting organs and grafting tissues into a patient" is the preamble, however the steps of the claimed method comprise regenerating an involuted thymus, intrathymic injection and transplanting organs or grafting tissue. One of the steps of claim 16 comprises restoring immune system function by regenerating the patient's involuted thymus. The MPEP states, a claim which fails to interrelate essential elements of the invention as defined by Applicants in the specification may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention (MPEP 2172.01). Regenerating the patient's involuted thymus is part of the steps of method claim 16. Contrary to Appellant's assertion, claim 16 does not recite active, positive steps, which delimit how a patient's involuted thymus is regenerated. The omitted steps of regenerating an involuted thymus are essential to the method of claim 16.

At the beginning of page 6 of the Brief, Appellant argues that the expression, "immunological equivalent" is frequently used in the literature, and means that the immunological equivalent material induces an immunological effect equivalent to a specific material, e.g., the tissue or organ to be transplanted into a patient. Appellant argues that those having ordinary skill in the art would not regard the expression immunological equivalent as a relative term and that a material either is or is not the immunological equivalent of the organs and/or tissue grafted into the patient. Appellant argues that the material either does or does not induce an immunological effect

equivalent to the tissue or organ to be transplanted and thus the term immunological equivalent is not a term of degree and therefore is not a relative term. Appellant states that regardless, the fact that claim language includes terms of degree and may not be precise does not automatically render the claim indefinite. Appellant cites Seattle Box Co. v. Industrial Crating and Packing, Inc. 731 F.2d 818, 221 USPQ 568 (Fed Cir. 1984). Appellant maintains that the specification states that "donor-specific cells or antigens that are the immunological equivalent of the tissue itself are materials that stimulate deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ and include endogenously-derived sample in the case of those with autoimmune disease". Appellant argues that the person of ordinary skill in the art are adequately informed by the specification, and would have been fully aware of what constitutes immunological equivalent materials within the context of the claimed invention.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. The section of the specification, which Appellant cites specifically states, "at this time, a surgeon skilled at thymic biopsy retrieval injects into the thymus an appropriate sample of the tissue or organ to be transplanted later, or injects any other donor-specific cells or antigens (for example, bone marrow cells) that are the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells otherwise responsible for rejecting the transplanted tissue or organ". "This tissue may be an endogenously-derived sample in the case of those with autoimmune disease" (specification, page 15, line 24-page 16, line 1). Thus, although the

specification provides examples of possible immunological equivalents, there is no unambiguous definition of what the term does and does not encompass.

Seattle Box Co. v. Industrial Crating and Packing, Inc. 731 F.2d 818, 221 USPQ 568 (Fed Cir. 1984) states, "when a word of degree is used, the district court must determine whether the patent's specification provides some standard for measuring that degree". "The trial court must decide, that is, whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification". The instant specification uses "immunological equivalent" in a sentence but fails to specifically teach the definition of "immunological equivalent". Appellant argues that the expression, "immunological equivalent" is frequently used in the literature, but fails to provide references where the term "immunological equivalent" is used and defined. The Examiner has not found an unambiguous definition of the term in the literature. The field of immunology is vast and encompasses many different types of viruses, cells, microbes, macrophages, lymphocytes, antibodies, antigens, organs, etc. The instant specification fails to define immunological equivalent and thus the term remains vague and indefinite.

At the top of page 7 of the Brief, Appellant cites the Examiner's 35 U.S.C. 112, second paragraph rejection made in the previous Office Action (13 January 2004, page 3). Appellant argues that while the Examiner never used the word "enablement" in the 35 U.S.C. 112, second paragraph rejection, the statement that "the steps of regenerating the involuted thymus have not been taught" implies lack of enablement. At page 8 of the Brief, Appellant continues to argue enablement.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The Examiner clearly made a 35 U.S.C. 112, second paragraph rejection. Thus there is no need for the Examiner to make any withdrawal. The Examiner used a form paragraph (paragraph 7.34.01) to make the instant rejection as is taught in MPEP 706.03(d). It appears that Appellant is confusing the rejection of claim 16 under 35 U.S.C. 112, second paragraph with the rejection of claims 16-22 and 32-34 under 35 U.S.C. 112, first paragraph. The Examiner recited references provided by Appellants to demonstrate lack of enablement for claims 16-22 and 32-34 in the previous Office Action (04 April 2003, pages 4-7). However, the recital of references in the 112, first paragraph rejection had no bearing on the 112, second paragraph rejection of claim 16.

At the bottom of page 8 to the top of page 9 of the Brief, Appellant argues that it was never asserted that the steps do not comprise the injection of the immunological equivalent of the organs or tissue to be transplanted into a patient's regenerated thymus. Appellant contends that the statement was that the steps do not merely comprise injecting the immunological equivalent into the regenerated thymus, but instead, first, require a step of restoring immune system function by regenerating the patient's involuted thymus. Appellant argues that they are claiming "a method for transplanting organs and grafting tissue into a patient" **not** "a method for regenerating an involuted thymus". At the bottom of page 9, Appellant states that the Examiner is attempting to argue that claim 16 is indefinite because it fails to set forth essential limitations relating to the step of regenerating the thymus. Appellant states that the Examiner's reasoning that additional limitations are required because the thymus must

be regenerated before the immunological equivalent can be injected in incorrect. Appellant argues that the claim clearly requires that the thymus must regenerated before the immunological equivalent material is injected. Appellant contends that this is also evident from the requirement that the immunological equivalent of the tissue or organ to be transplanted is injected into the regenerated thymus.

Appellant's arguments have been fully considered but are not deemed to be persuasive. Claim 16 omits matter disclosed to be essential to the invention as described in the specification. Appellant repeatedly states that the invention is "a method for transplanting organs and grafting tissue into patient" not "a method of restoring immune function by regenerating a patient's involuted thymus". The Examiner understands the invention to be a process for preparing patients for organs transplants or tissue grafts, which would reduce the risk of organ transplant or tissue rejection. The claimed invention comprises steps that must be employed to avoid risk of rejection. The first step comprises regenerating a patient's involuted thymus, in order to restore immune function. Regenerating the involuted thymus is essential to the claimed invention. The next step (injecting the immunological equivalent) cannot take place until the involuted thymus is regenerated. The MPEP states that a claim which fails to interrelate essential elements of the invention as defined by Applicants in the specification may be rejected under 35 USC 112, second paragraph, for failure to point out and distinctly claim the invention (MPEP 2172.01).

At the top of page of 10 of the Brief, Appellant argues that the claim is not indefinite merely because it does not include further limitations that more specifically

restrict the technique used for regenerating the thymus. Appellant asserts that while those having ordinary skill in the art would be provided with an opportunity to more easily avoid infringement if the claims were more narrowly directed to regenerating the patient's thymus by administering HGH, HGH analogs, HGH precursors, HGH metabolites, HGH releasers, HGH mimics, or mixtures thereof, as required in claim 20, the standard by which definiteness is determined is not based on the ease by which infringement can be avoided. Appellant argues that an important pioneering invention of the type claimed cannot be rejected as being indefinite merely because it is not written narrowly enough to allow competitors to easily avoid infringement. Appellant asserts that those having ordinary skill in the art can determine whether a patient's involuted thymus is regenerated prior to injection of the immunological equivalent tissue or organ into the patient's regenerated thymus. Appellant states that the public can determine the boundaries of what constitutes infringement. At the bottom of page 10 of the brief, Appellant argues that the requirement that steps essential to practicing the invention must not be omitted from the claims, is limited to the situation in which the claim omits matter disclosed to be essential to the invention as described in the specification or in other statements of record. Appellant cites *In re Mayhem, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).* Appellant reiterates that the invention is "a method for transplanting organs and grafting tissue into patient", **not** "a method of restoring immune function by regenerating a patient's involuted thymus". Appellant argues that there is not any statement in the specification or on the record that would indicate that the Appellant regards a particular technique of regenerating the thymus to be essential to the claimed

invention. Appellant maintains that at page 17, lines 1-4, the specification states, "in broader aspects of thymic regeneration to facilitate thymic injection and subsequent organ and tissue transplantation, alternative methods for regenerating the thymus can be utilized". Appellant argues that there are other techniques that may utilized in the broader aspects of the invention and that claim 16 does not omit essential matter.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The instant rejection is not based on infringement. Claim 16 omits matter disclosed to be essential to the invention as described in the specification. The claim depends on a recited property. The claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. Appellant argues that there are other techniques that may utilized in the broader aspects of the invention and that claim 16 does not omit essential matter. Appellant recites compounds for regenerating the patient's thymus in claim 20. However, the recitation of compounds in claim 20 does not cure the deficiency in the base claim 16.

At the top of page 11 of the Brief, Appellant argues that the fact that the specification does not use the word "definition" in defining the meaning of the expression "immunological equivalent" does not mean that the specification fails to define the term. Appellant cites the passage in the specification where the term "immunological equivalent" is used. At the top of page 12 of the Brief, Appellant maintains that when properly read in the context of the specification, it is clear to one having ordinary skill in the art that Appellant is defining the expression "immunological

equivalent" as a material that is the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ. Appellant states that in addition to expressly defining the meaning of the term "immunological equivalent", the Appellant has provided several specific examples to further illustrate the meaning of the term and define the invention with reasonable certainty such that the public is fairly put on notice as to the metes and bounds of the invention. Appellant cites MPEP 2173.02.

Appellant's arguments have been fully considered but are not deemed to be persuasive. Appellant uses the term "immunological equivalent" in the definition of immunological equivalent, which is not helpful. Appellant defines immunological equivalent as "a material that is the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ". This definition sets forth what "immunological equivalent" must do, but not what it is. Immunological equivalent has not been defined and cannot be discerned from the context of the specification. Furthermore, no evidence of record has been provided by Appellant to further illustrate the meaning of the term and define the invention with reasonable certainty such that the public is fairly put on notice as to the metes and bounds of the invention.

Appellant concludes this section by urging that the rejection of claim 16 under 35 U.S.C. § 112, second paragraph is inappropriate and must be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

B. Claim Rejections Under 35 U.S.C. 112, First Paragraph

At the bottom of page 13 of the Brief, Appellant states, "the test of enablement is whether one reasonably skilled in the art could make or use the invention form the disclosure in the patent application coupled with information known in the art without undue experimentation". "A patent need not teach, and preferably omits, that which is well known in the art". Appellant cites case law *In re Buchner, 929 F.2d 660, 661, 18 USPQ.2d 1331, 1332 (Fed. Cir. 1991);* Hybritech, Inc. v. Monoclonol Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 US 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The Examiner takes no issue with Appellant's characterization of the legal requirements of 35 USC 112, first paragraph.

At page 14 of the Brief, Appellant cites the Examiner's 112, first paragraph rejection from the previous Office Action (04 April 2003). Appellant argues that the Examiner has admitted that both Greenstein *et al.* and McCormick *et al.* references teach that regeneration of an involuted thymus is well known to those possessing ordinary skill in the art. Appellant maintains that the instant specification teaches techniques for regenerating an involuted thymus. Appellant cites pages in the specification. Appellant contends that the specification, the evidence of record and the Examiner's own statements show that regeneration of an involuted thymus is well known to those having ordinary skill in the art and is adequately described in the

specification to provide enablement those having ordinary skill in the art. Appellant states, "in view of the fact that the Appellant provided a specific treatment regimen for regenerating an involuted thymus, and in view of the fact that the prior art discloses similar techniques for regenerating a thymus, it is respectfully submitted that the disclosure coupled with information known in the art would provide the necessary enablement for regenerating a human thymus".

Appellant's arguments have been fully considered but are not deemed to be persuasive. Greenstein and McCormick disclose the obstacles encountered by those in the art attempting to regenerate an involuted thymus. Specifically, Greenstein demonstrates that regeneration of an age-involuted thymus can be accomplished in rats using an analogue of luteinizing hormone-releasing hormone (LHRH), however, the LHRH analogue also reduced testosterone concentrations. McCormick teaches that regeneration of an age-involuted thymus can be accomplished in rats using growth hormone, however, there was no significant improvement of cellular immune function and there was a high incidence of hepatic tumors in the growth hormone treated mice. While the literature submitted by Appellant teaches regeneration of age-involuted thymus, the experiments were only executed in rats, which are not representative of the scope of the claims, there was no significant improvement of cellular immune function and there were harmful side effects (reduced testosterone concentrations, hepatic tumors). Thus the literature of record teaches an art, which reports the incidence of harmful side effects, and is unpredictable regarding improvement of cellular immune function. **One of the limitations of the instant claims is restoring immune function**

(Emphasis added). In addition, harmful side effects affects the patient's immune system function. This is important for the claimed method. For example, a patient's immune system function affects organ transplant or tissue graft operations. Most importantly, the instant invention involves the combination of techniques comprising restoring immune system function by regenerating the patient's involuted thymus; injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus (or, in the case of bone marrow cell, peripherally); and transplanting said organ or grafting said tissue. Neither the specification nor the literature of record teach the enablement of the instant invention, since these goals (restoring immune function and regenerating a thymus) have not been accomplished.

At page 15 of the Brief, Appellant states that a surgeon skilled at thymic biopsy retrieval would know how to achieve intrathymic injection without undue experimentation, and a skilled transplant surgeon would know how to transplant an organ or graft a tissue without undue experimentation. Appellant argues that each of the individual steps of the claimed method may be achieved by those having ordinary skill in the art without undue experimentation. Appellant argues that the Examiner has admitted the same. Appellant cites the Examiners 112, first paragraph from the previous Office Action (13 January 2004). Appellant argues that normally if all of the steps of a claimed process are enabled, the claimed process is enabled. Appellant states that the Examiner has taken the position that despite the fact that each of the individual steps are enabled, somehow the claimed method is not enabled. Appellant states that there is not any legal requirement that the Appellant prove with absolute certainty that the

claimed method would be successful in all cases. Appellant asserts that they need not have actually reduced the invention to practice. Appellant states that the mere fact that something has not previously been done is not, in itself, a sufficient basis for rejection. Appellant cites Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQZd 1302, 1304 (Fed.Cir. 1987) and *In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325(CCPA 1956).* At the beginning of page 16 of the Brief, Appellant states that the Examiner has admitted that each of the individual steps are enabled in the prior art. Appellant argues that there is not any reasonable doubt that those having ordinary skill in the art could restore immune function by regenerating a patient's involuted thymus and that this is clearly established in the prior art of record. Appellant contends that they have submitted evidence proving that the disclosed HGH therapy is effective for almost doubling the functional thymic mass of Appellant's own thymus. Appellant argues that those having ordinary skill in the art would expect that a doubling in functional thymic mass would result in an increase in thymic function. Appellant states that they have established with reasonable certainty that the disclosed treatments are effective for restoring immune function by regenerating a patient's involuted thymus. Appellant asserts that it would be absurd to question whether those having ordinary skill in the art were capable of injecting an immunological equivalent of the tissue or organ to be transplanted into a thymus, or whether those having ordinary skill in the art were capable of transplanting an organ or grafting tissue. Appellant argues that they should not be expected to prove or demonstrate universally accepted common knowledge. Appellant states that the evidence of record clearly shows that the claimed method can be performed based on

Appellant's disclosure and what is well known those having ordinary skill in the art, without undue experimentation.

Appellant's arguments have been fully considered but are not deemed to be persuasive. Appellant argues that normally if all of the steps of a claimed process are enabled, the claimed process is enabled. It appears that Appellant is arguing enablement by taking apart the different steps of the instant invention and using references to support enablement for the entire invention. **However, the enablement of the invention is based on the entire method steps taking place in a patient, not just the parts of the invention** (Emphasis added). Appellants have not demonstrated that the combined methods are enabled in a patient. Moreover, the individual steps of the invention are not predictable in a patient. The reference submitted by Appellant demonstrate that regeneration of age-involuted thymus (step 1 of the invention) and intrathymic injection (step 2 of the invention) were only executed in rats. Furthermore, there was no significant improvement of cellular immune function and harmful side effects such as hepatic tumors occurred upon regeneration of age-involuted thymus in rats.

The Examiner agrees with Appellant's assertion that the mere fact that something has not previously been done is not, in itself, a sufficient basis for rejection and that they need not have actually reduced the invention to practice. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. However, lacking a working example is a factor to be considered, especially in a case

involving an unpredictable and undeveloped art. Regenerating a patient's involuted thymus and intrathymic injection are unpredictable and undeveloped arts. The Fahy declaration, which Appellant alludes to, states that in response to hGH and DHEA, the percent increase in total thymic lymphoid (functional) mass was 92%. However, Goff *et al.* (reference submitted by Appellant) states a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function; immunological or endocrine function must be assessed. Furthermore, the Fahy Declaration fails to demonstrate that immune system function has been restored, which is a limitation of the instant claims.

At the bottom of page 16 of the Brief, Appellant cites the Examiner 112, first paragraph rejection. Appellant argues that anyone reading the specification would understand that it teaches more than only administration of arginine and DHEA and HGH and DHEA. At the top of page 17 of the Brief, Appellant states that the specification discloses additional techniques for thymic regeneration and that a single technique for thymic regeneration would be sufficient. Appellant argues that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. Appellant asserts that the failure to disclose other techniques by which the claimed invention may be practiced does not render a claim invalid under 35 U.S.C. 112. At the middle of page 17 of the Brief, Appellant states that the Examiner argued that the specification does not provide guidelines to determine thymic atrophy or involution. Appellant argues that they are not

claiming a method for determining thymic atrophy or involution and that the techniques for determining thymic atrophy or involution are well known to those having ordinary skill in the art need, need not be described and are preferably omitted from the specification. Appellant argues that thymic atrophy or involution is the norm for people age 40 and over and that in the absence of unusual medical conditions or the administration of substances that induce thymic regeneration, elderly patient would almost certainly have an involuted thymus, such that determination of thymic atrophy or involution is unnecessary. Appellant argues that in the case of individuals under the age of 20, it is extremely likely that that the claimed method would be unnecessary. Appellant argues that in the case of individuals between the ages of 20 and 40, it may be necessary or desirable to determine the extent of atrophy or involution before practicing the claimed method and can be achieved by using techniques that are well known to those having ordinary skill in the art. Appellant asserts that the specification expressly discloses that thymic regeneration may be verified by magnetic resonance imaging. Magnetic resonance imaging has been well known by those having ordinary skill in the art and has been routinely used for decades.

The Examiner agrees with Appellant's assertion that the enablement requirement of 35 U.S.C. 112 is met if the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. The Examiner also agrees with Appellant's assertion that failure to disclose other techniques by which the claimed invention may be practice does not render a claim invalid under 35 U.S.C. 112. However, as was stated above, the instant

specification fails to disclose any method for making and using the claimed method. Appellant again argues that a method for determining thymic atrophy or involution is not being claimed. This is not found persuasive. While determining thymic atrophy or involution is not being claimed, part of the invention step requires regenerating an involuted thymus. Because the instant claims are drawn to "any patient's" involuted thymus, one would have to determine whether the thymus is involuted before it can be regenerated. The instant claims fail to recite an age limitation and thus the claims encompass all patients, not just people age 40 and over.

Appellant states that it is extremely unlikely that the claimed method would be necessary in individuals under the age of 20. This is not found persuasive because the instant claims recite "involuted thymus" not "age-related thymic involution". Thymic atrophy or involution can occur in individuals under the age of 20 for other medical reasons such as hypothyroid conditions or cancer. Consequently, it would be necessary to determine thymic atrophy or involution for methods, which fail to recite limitations for age population and types of thymic atrophy. Appellant argues that techniques for determining thymic atrophy or involution are know in the art and cites page 15, lines 18-20 in the instant specification. This is not found persuasive. The specification states, "after thymic regeneration, the thymus should be imaged (preferably by magnetic resonance imaging, though other methods are also acceptable) to verify regeneration and thymic location". The specification fails to provide parameters for discerning initial thymic atrophy or involution. The specification discloses one method for viewing potential thymic regeneration but fails to teach limitations or factors to verify

regeneration.

At page 18 of the Brief, Appellant quotes the Examiner. Appellant argues that the statement, "the specification fails to teach that a thymus can be regenerated upon administration of human growth hormone and DHEA or human growth hormone and chromium picolinate in a patient" is incorrect. Appellant states that evidence was submitted to the Examiner and published in a peer-reviewed scientific literature, showing that the exact instructions provided for thymic regeneration in the specification involving the administration of human growth hormone and DHEA did in fact double the functional mass of the Appellant's own thymus. Appellant cites *In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645, (CCPA 1970),* in response to the Examiner's statement that, "the disclosure does not provide immunological or endocrine assays or employ experiments such as magnetic resonance imaging or morphology studies which would discern that a thymus has been regenerated". Appellant asserts that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. Appellant argues that the specification provides specific direction and guidance for administering HGH in combination with DHEA to achieve thymic regeneration and has submitted a declaration showing that the technique disclosed in the specification was successfully employed for nearly doubling the functional mass of Appellant's own thymus. At the bottom of page 18 of the Brief, Appellant quotes the Examiner. In response to the Examiner's statement that, "the specification provides no guidance or working examples for intrathymic injection", Appellant argues that

intrathymic injection is well known to those having ordinary skill in the art. Appellant states that a patent need not teach and preferably omits what is well known in the art. At the top of page 19 of the Brief, Appellant argues that the fact that intrathymic injection is well known to those having ordinary skill in the art is demonstrated by the fact that there are dozen of issue patents disclosing intrathymic injection, including U.S. Patent 4,263,279. Appellant states that there cannot be any serious dispute as to whether those having ordinary skill in the art would be capable of achieving intrathymic injection without undue experimentation. Appellant states that there is not any doubt that techniques for transplanting organs and grafting tissue are well known to surgeons possessing ordinary skill in the art, and that such surgeons routinely perform organ transplants and tissue grafts. Appellant asserts that the claims are enabled with respect to the step of transplanting said organ or grafting said tissue.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The instant specification and The Fahy Declaration under 37 CFR 1.132 (filed 29 August 2003) fail to teach that a thymus can be regenerated upon administration of human growth hormone and DHEA or human growth hormone and chromium picolinate. Appellant argues that evidence was submitted showing that the administration of human growth hormone and DHEA did in fact double the functional mass of the Appellant's own thymus. Appellant argues that the specification need not contain an example providing immunological or endocrine assays or MRI or morphology studies. Appellant cites *In re Borkowski* to support this assertion. However, Goff *et al.* (reference cited by Appellant), teach that a change (or lack of change) in thymic

morphology does not prove increased or decreased thymic function; immunological or endocrine function must be assessed.

Appellant argues that intrathymic injection is well known to those having ordinary skill in the art and cites U.S. Patent 4,263,279. This is not found to be persuasive because U.S. Patent 4,263,279 teaches pharmaceutically active compositions containing adriamycin and daunomycin. The instant patent contains one sentence regarding intrathymic injection, "in addition a lymphoma induced in Lewis rats by the intrathymic injection of murine radiation leukemia virus was also used" (column 3, lines 35-36). Appellant states that transplanting organs and grafting tissue are well known to surgeons possessing ordinary skill in the art. Appellant asserts that the claims are enabled with respect to the step of transplanting said organ or grafting said tissue. The Examiner agrees that transplanting said organ or grafting said tissue is enabled in humans. The argument is not directed to the enablement of organ transplant or tissue grafting in humans. **The Examiner is questioning whether the combination of all of three steps is enabled in humans (i.e. can a patient's immune system function be restored by having an involuted thymus regenerated, then undergo an intrathymic injection of an immunological equivalent and then an organ transplant/tissue graft)** (Emphasis added).

Appellant has repeatedly stated that, "a specification does not disclose what is well known to those having ordinary skill in the art", "intrathymic injection is well known", "transplanting organs and grafting tissue are well know". As was stated above, it appears that Appellant is arguing the enablement of each step of the invention and

applying it to the total invention. This is not found persuasive. **The fact that organ transplant and tissue grafting is known in the art for humans and thymus regeneration and intrathymic injection has been shown in rats, does not mean that the entire combination is enabled in humans** or any other patients (Emphasis added). Also, the evidence of record shows the obstacles of restoring immune system function, regenerating an involuted thymus and injecting immunological equivalent, all of which are required by the claims.

At the bottom of page 19 of the Brief, Appellant cites the Examiner's rejection, "the specification does not consider factors such as rejection, age-related thymic involution versus other types of thymic involution, the side effects of immunosuppressants, ALS versus CsA, the high incidence of tumors and other side effects associated with GH". Appellant once again argues that a patent need not teach, and preferable omits which is well known in the art. Appellant argues that the Examiner has failed to explain why age-related thymic involution versus other types of thymic involution is relevant to the claimed invention. Appellant states that they are not aware of any pathological conditions that would cause any evidence of such pathological process that would cause irreversibly involuted thymus and the Examiner has failed to provide evidence of such pathological processes that would cause irreversible thymic involution. Appellant argues that there is not any evidence that there is an issue relating to age-related thymic involution versus other types of thymic involution. At page 20 of the Brief, Appellant argues that the side effects of immunosuppressants such as ALS and CsA are well known in the art. Appellant states that issues relating to the side

effects of immunosuppressants are not relevant to the claimed invention, which does not require or exclude the use of immunosuppressants and does not promise a complete absence of side effects. Appellant asserts that the Examiner's reference to a high incidence of tumors is not relevant to the claimed invention, which does not exclude the possibility of tumors. Appellant argues that there is an absence of any evidence that growth hormone treatment causes a high incidence of hepatic tumors. Appellant cites McCormick *et al.* (reference provided by Appellant). Appellant argues that McCormick *et al.* clearly stated that their experiments did not include a large enough population to make a determination as to whether growth hormone treatment causes hepatic tumors in the particular mice used in the experiments. Appellant contends that the claims are not directed to a method for transplanting organs or tissues with a guarantee that the patient will not develop tumors. Appellant argues that the claims are not directed to a method for transplanting organs and grafting tissue with a guarantee that there will never be any undesirable side effects associated with growth hormone therapy. Appellant argues that each of the factors that allegedly have not been considered in the specification are well known to those having ordinary skill in the art and/or are not relevant to enablement with respect to the claimed invention. Appellant submits that the Examiner has not provided any evidence or reasoning that would suggest that undue experimentation is needed. Appellant asserts that the Examiner has admitted that the individual steps are enabled. Appellant states that the patent laws do not require that any invention must be free of all drawbacks, side effects and complications.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The Examiner stated the drawbacks, side effects and complications associated with thymus regeneration, intrathymic injection and organ transplant/tissue grafting by using the references of record and the knowledge to those skilled in the art. The Examiner was trying to make the point that each procedure alone is wrought with a high level of unpredictability and experimentation. The drawbacks, side effects and complications affect the enablement of the instant invention. As was stated earlier, side effects can affect a patient's immune system function and complicate organ transplant/tissue graft operations. Organ transplant and tissue grafting, while enabled in humans, can be variable.

Appellant asserts that issues relating to the side effects of immunosuppressants are not relevant to the claimed invention. Appellant is incorrect. Immunosuppressants are necessary for any type of organ transplant or tissue graft. Perico *et al.* (reference submitted by Appellant) disclosed that cyclosporin (CsA) and steroids used to inhibit T cell activation and to deplete them from peripheral circulation *also induce changes in the structure and function of the thymus, which included a decrease in thymus epithelial and cortical cells.* Perico *et al.* does not conclusively demonstrate that immunosuppressive drugs do not interfere with the functional properties of the thymus. This is important because immunosuppressants, which are needed for transplants and grafts could affect a patient's thymus.

The Examiner discussed age-related thymic involution versus other types of thymic involution because the instant claims fail to recite an age limitation for the patient

population. Thus not all of the patient population, as defined by the claim, would have an involuted thymus (i.e. young patients). Furthermore, the instant claims fail to recite the type of involuted thymus (i.e. age-related thymic involution or other types of thymic involution). Thymic atrophy or involution can occur in individuals under the age of 20 for medical reasons such as hypothyroid conditions or cancer. The instant claims encompasses both age-related and other types of thymic involution. The specification fails to address whether a patient with a different type of thymic involution (i.e. not age-related) could undergo thymic regeneration.

Appellant argues that there is an absence of any evidence that growth hormone treatment causes a high incidence of hepatic tumors, but fails to address the last sentence of the paragraph cited from McCormick *et al.*, which states, "however, given the absence of tumors in placebo treated mice, these results do indicate that a correlation between growth hormone and hepatic tumors is likely". McCormick *et al.* maintains, "thymus mass was increased and the morphological integrity of the thymus was restored in the growth hormone treated animals". "However, we found no significant improvement in the assays of cellular immune function". "A high incidence of hepatic tumors was noted in the growth hormone treated mice" (McCormick *et al.*, page 20, lines 16-19). Thus, not only is McCormick stating that no significant improvement in the assays of cellular immune function was observed, but the incidence of hepatic tumors was elevated. The Examiner finds Appellant's statement, "the claims are not directed to a method for transplanting organs or tissues with a guarantee that the patient will not develop tumors" disconcerting. Appellant has disregarded the salient

points of McCormick *et al.*, no significant change in immune function, which is a limitation of the instant claims, and the risk of developing liver cancer.

Appellant is correct in the assertion that the patent laws do not require that any invention must be free of all drawbacks, side effects and complications, but as was stated above, drawbacks, side effects and complications affect the enablement of the instant invention. The subject matter sought to be patented as defined by the claims must be supported by an enabling disclosure. The Examiner is questioning whether the combination of all of three steps is enabled in a patient. Each procedure alone is difficult, thus there is no doubt that the invention which combines all three procedures would be extremely complex. A large quantity of experimentation would be necessary to execute the combination of all three procedures: regenerate an involuted thymus and administer an intrathymic injection and transplant an organ or tissue in a patient. The specification lacks direction and guidance for this invention. There is an absence of working examples directed to the invention. The prior art establishes that regeneration of age-involuted thymus and intrathymic injection has only been executed in rats. The prior art establishes the incidence of hepatic tumors, and the unpredictability regarding improvement of cellular immune function upon administration of growth hormone in thymic regeneration. Lack of improvement of cellular immune function and harmful side effects would definitely affect the enablement of the instant method.

At the bottom of page 21 of the Brief, Appellant argues that the Examiner has admitted that the individual steps are known in the art. Appellant asserts that the Examiner has mischaracterized the invention and point of novelty. Appellant states that

the point of novelty relates to preparing a patient for organ or tissue transplant by stimulating deletion or anergy of the cells otherwise responsible for rejecting the transplanted tissue or organ and that the method is not limited to humans, but would work equally well in other animals. At the top of page 22 of the Brief, Appellant states that the Examiner appears to be arguing that while the individual steps are enabled, the combination is not enabled. Appellant argues that while there may be hypothetical examples of methods that are not enabled even though the individual steps comprising the method are enabled, these examples would be limited to situations where there is an apparent conflict or impossibility. Appellant contends that there is not any such apparent conflict or impossibility in the claims at issue. Appellant maintains that those having ordinary skill in the art would understand that a patient's thymus might be regenerated, that a sample of material immunologically equivalent to an organ may be transplanted into the patient. Appellant maintains that those having ordinary skill in the art would understand that the combination of steps is possible, and would expect, from Appellant's disclosure, that the combination would achieve the intended result, i.e. lower incidence of rejection.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The Examiner has not mischaracterized the invention and the point of novelty. Novelty is not an issue under 35 USC 112, first paragraph. The Examiner understands the invention to be a process for preparing patients for organs transplants or tissue grafts to reduce the risk of organ transplant or tissue rejection. The claimed invention comprises steps that must be employed to avoid risk of rejection. The

Examiner understands that "a method for transplanting organs and grafting tissues into a patient" is the preamble of the method, which comprise the steps of regenerating an involuted thymus, intrathymic injection and transplanting organs or grafting tissue.

Appellant asserts that the method is not limited to human and would work equally well in other animals. This is not found to be persuasive. The instant claim recites the limitation "patient". The Examiner understands that while the claims are interpreted in light of the specification, limitations from the specification are not read into the claims In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, the instant specification states, "the present invention includes a method for regenerating the **human thymus** to allow intrathymic transplantation and thereby the elimination of organ and tissue rejection" (specification page 1, lines 5-7). Humans are clearly a preferred embodiment. Also, ambiguous evidence relied upon by Appellant regarding rats, is not commensurate in scope with the claims.

As was stated above, each step of the claimed method is difficult and wrought with elements of unpredictability. The instant invention is extremely complex. A large quantity of experimentation would be necessary to execute the combination of all three procedures in a patient. The specification lacks direction and guidance for this invention. There is an absence of working examples directed to the instant invention. The specification fails to teach parts of the claimed invention such as a regenerated thymus or restored immune system function. The specification fails to teach that the claimed method actually lowers the incidence of organ transplant or tissue graft rejection. As was previously stated, the specification need not contain examples if the invention is

otherwise disclosed in such a manner where one skilled in the art could practice without an undue amount of experimentation. Lacking working examples is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. In addition, the prior art establishes that regeneration of age-involuted thymus and intrathymic injection has only been executed in rats. The prior art establishes the unpredictability regarding improvement of cellular immune function upon administration of growth hormone in thymic regeneration.

At the middle of page 22 of the Brief, Appellant states that the Examiner has taken the position that Dr. Fahy's Declaration is insufficient to over the lack of enablement rejection because it only shows an increase in functional thymic mass, not an increase in thymic function. Appellant argues that the Examiner has expressed doubts based on the Goff reference, by relying on Goff's statement that "a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function; immunological or endocrine function must be assessed". Appellant argues that this quote is an inappropriate generalization and mischaracterization of the Goff study, and is not based on any finding of Goff *et al.* that thymic regeneration failed to result in increased thymic function. Appellant argues that the opposite is true. Appellant asserts that the rest of the Goff reference teaches there is an increase in thymic function associated with increased thymic mass. Appellant submits that Goff *et al.* used the production of thymulin by the thymus as their measurement of the restoration of thymic function. Appellant cites the abstract of Goff *et al.* At page 23 of the Brief, Appellant argues that while there may have been some question before Goff's study as to whether

an increase in thymic function associated with an increase in thymic mass, the doubts were put to rest by Goff *et al.*, who showed that there is definitely an increase in thymic function associated with an increase in thymic mass. Appellant argues that the Goff *et al.* reference reinforces Appellant's claim that immune system function may be restored by regenerating a patient's involuted thymus.

The Examiner understands that Goff *et al.* use the production of thymulin by the thymus as their measurement of restoration of thymic function. Goff *et al.* state that treatment with growth hormone may enhance immune function in aged individual by causing a sustained elevation of plasma thymulin concentration and perhaps will stimulate increases in other thymic hormone concentrations as well (Goff *et al.* page 585, last sentence). Appellant argues that "the Goff study showed that ....in old-age dog population, immune function was improved even before thymic regeneration took place". Appellant argues that this implies that by the time thymic regeneration is actually observed, improved immunological function is to be expected, just as taught by the Appellant's disclosure. Appellant has failed to cite where Goff *et al.* teach this. The Examiner cannot locate this teaching and thus cannot rebut the assertion.

Appellant argues that the rest of the Goff reference teaches that there is an increase in thymic function associated with increased thymic mass. Appellant is incorrect. Goff *et al.* states that in middle-age but not old-age dogs, bovine growth hormone treatment resulted in rejuvenation of thymic morphological features as determined by stereological and histomorphological procedures. Goff et al teach that improved thymic morphology was observed in four of the five bovine growth hormone

(bGH) treated middle-age dogs. One of the five control dogs (dogs that did not receive bGH) had a better than expected morphology. Goff *et al.* state that there is normal variation in the morphology of the thymus in individuals of the same age. Factors which can cause changes in thymic morphology include stress, viral infections, and other hormones addition to GH (Goff *et al.*, page 585, 1st paragraph).

Most importantly, Goff *et al.* state that in contrast to the middle-age dogs there were no detectable histomorphological changes in the thymus of the old-age dogs (Emphasis added). See Goff *et al.*, second paragraph of page 585 of the reference. Goff *et al.* teach that a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function, immunological or endocrine function must also be assessed. Goff *et al.* test thymic function in the old-age dogs by assessing endocrine function. Goff *et al.* teach that even in the oldest dogs studied (which had no change in thymic morphology) had consistent increases in plasma thymulin concentrations.

Appellant has misinterpreted the teachings of Goff *et al.* Goff *et al.* does not teach that there is definitely an increase in thymic function associated with an increase in thymic mass. If that were the case, the old-age dogs would have histomorphological changes in the thymus. This was not the case. **Goff *et al.* had to assess endocrine functions of the old-age dogs** (Emphasis added). **From that study, Goff *et al.* discerned that old-age dogs had increases in plasma thymulin concentrations even though there were no changes in morphology** (Goff reference, page 585, 2nd paragraph and Figure 4).

Contrary to Appellant's assertion, the point that Goff *et al.* were making was thymic function cannot be assessed by morphology alone. This was evident from the experiments where one of the control dogs had a better than expected morphology, although that dog never received growth hormone. It was also evident from the experiments in the old-age dogs where increases in thymulin concentrations were detected although there were no changes in thymus morphology. Moreover, Goff *et al.* states that stress, viral infections, and other hormones in addition to growth hormone can affect thymus morphology. **Thus, it would be obvious to one skilled in the art that a change or lack of a change in thymic morphology would not prove increased or decreased thymic function, other biological functions would need to be assessed** (Emphasis added). Neither the instant specification nor the Fahy Declaration teach the assessment of immunological or endocrine functions.

At the bottom of page 23 of the Brief, Appellant states that the claims are not directed to processes for increasing or decreasing insulin levels. Appellant argues that the specification includes working examples that show that co-administration of DHEA prevents an increase in insulin levels normally associated with HGH therapy. Appellant argues that this is shown in experiments 1 and 2. Appellant argues that the Examiner's statements regarding insulin level are not relevant to the claimed method, and that they have demonstrated that co-administration of DHEA prevents the increase in insulin levels normally associated with HGH therapy. At the top of page 24 of the Brief, Appellant states that the wealth of scientific evidence strongly suggests and demonstrates that increased thymic mass results in increased function. Appellant

asserts that the Goff *et al.* reference states that increasing thymic mass causes increases thymic function. Appellant asserts that they know of no valid evidence that thymic regeneration has ever been observed without an accompanying increase in thymic function. Appellant states that the McCormick reference described animals with tumors whose immune function was badly skewed as a result of tumor growth and cannot be considered representative of the normal states. Appellant submits that McCormick did report signs that immune function was returning. At the middle of page 24 of the Brief, Appellant states that those skilled in the art would have known how to achieve intrathymic injection in laboratory animals as admitted by the Examiner. Appellant submits that there is not any reason to believe that those having ordinary skill in the art would be incapable of achieving the same in humans. Appellant argues that the burden should be placed on the Examiner to show why those skilled in the art are able to achieve intrathymic injection in a laboratory animal but incapable of achieving the same in human. Appellant asserts that the claims are not limited to the treatment of humans.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The instant specification teaches that the administration of human growth hormone (HGH) is known to decrease the body's responsiveness to insulin. The Examiner believes insulin levels are relevant to the claimed method because elevated insulin has been linked in many studies to the development of atherosclerosis, hypertension and heart disease (specification; page 2, lines 6-18). These conditions would affect the enablement of the instant claimed method.

Appellant argues that Experiments 1 and 2 of the specification show that co-administration of DHEA prevents the increase in insulin levels normally associated with HGH therapy. This statement is incorrect. Experiments 1 and 2 of the specification demonstrate that DHEA prevents the increase in insulin levels upon the administration of arginine. However, arginine is an HGH releaser, not a human growth hormone. The specification does not teach the administration of HGH. The Fahy declaration teaches the co-administration of DHEA and HGH, but fails to disclose the insulin levels. **Thus, neither the specification nor the Fahy Declaration teach that the co-administration of DHEA prevents the increase in insulin levels associated with HGH** (Emphasis added).

Appellant is correct in stating that the instant claims are not directed to processes for increasing or decreasing insulin levels. However, the increased likelihood of developing heart disease and hypertension are factors to consider. These conditions affect the patient's immune system function, which is important in organ transplant or tissue graft operations. The Fahy declaration only teaches the co-administration of DHEA and HGH. The Fahy declaration fails to teach intrathymic injection and organ transplant/tissue graft.

The Examiner has already addressed Appellant's arguments regarding the Goff *et al.* reference. The salient teachings of Goff *et al.* were that stress, viral infections, and other hormones in addition to growth hormone can affect thymus morphology. A change (or lack of change) in thymic morphology does not prove increased or decreased thymic function, immunological or endocrine function must also be assessed.

Appellant states that the McCormick reference described animals with tumors whose immune function was badly skewed as a result of tumor growth and cannot be considered representative of the normal states. It is unclear to the Examiner what Appellant means by, "representative of the normal states". The McCormick reference investigated the ability of growth hormone to rejuvenate the age-involuted thymus and to restore the senescent immune response. The instant invention employs the use of growth hormone to restore immune system function by regenerating a patient's involuted thymus. The McCormick reference teaches the high incidence of hepatic tumors in the growth hormone treated mice. Appellant's statement is incongruous with the teachings of the McCormick reference and the instant invention.

Appellant states that the burden should be placed on the Examiner to show why those skilled in the art are able to achieve intrathymic injection in a laboratory animal but incapable of achieving the same in human. There are many situations where a technique has been accomplished in an animal but not in a human. Furthermore, the invention is just not intrathymic injection but restoring a patient's immune system function by having an involuted thymus regenerated, intrathymic injection and organ transplant/tissue graft. The Examiner has already discussed Appellant's statement that the claims are not limited to the treatment of humans. The instant claims recite the limitation, "patient". Furthermore, the instant specification never discloses or teaches the instant invention in animals.

At the bottom of page 24 to the top of page 25 of the Brief, Appellant cites the Examiner's rejection. Appellant argues that the claims are not limited to the treatment

of human, but are equally applicable to animal patients. Appellant argues that regardless of whether intrathymic injection is known in humans or not, it does not require undue experimentation to extend intrathymic injection from animals to humans. Appellant states that most of the Examiner's arguments are unsupported by any evidence of record, and are contrary to the evidence of record. At the bottom of page 25, Appellant argues that the reference the Examiner relied on for showing that there is some doubt as to whether increasing thymic mass results in increased thymic function, actually demonstrates an increase in thymic function resulting from an increase in thymic mass, thus supporting enablement for the step of restoring immune system function by regenerating the patients involuted thymus. Appellant states that the Examiner has admitted that the step of injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus is known in the art with respect to laboratory animals. Appellant argues that there cannot be any doubt that those skilled in the art would be capable of achieving the same result in humans without undue experimentation. Appellant states that there cannot be any doubt whether surgeons skilled in the art of organ transplantation and tissue grafting would be capable of performing these activities after restoring immune function by regenerating a patient's involuted thymus and injecting the immunological equivalent of the tissue or organ to be transplanted into the regenerated thymus.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The Examiner has already addressed Appellant's arguments regarding the Goff *et al.* reference. Goff *et al.* teach that a change (or lack of change) in thymic

morphology does not prove increased or decreased thymic function, immunological or endocrine function must also be assessed. Stress, viral infections, and other hormones in addition to growth hormone can affect thymus morphology. Neither the specification nor the Fahy declaration disclose where immunological or endocrine functions were assessed to discern thymic function and thus restored immune system function.

The Examiner did not say, "the step of injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus is known in the art with respect to laboratory animals" (Emphasis added). The Examiner does not understand the term "immunological equivalent", hence the 112, second paragraph rejection. The Examiner stated that "intrathymic injection is known in the art with respect to laboratory animals" and the "combination of intrathymic injection and organ transplant/tissue graft" is known in the art with respect to laboratory animals. Odorico *et al.* (reference submitted by Applicant) teach the intrathymic injection of donor spleen cells and the concurrent administration of anti-lymphocyte serum before cardiac allografts in rats. However, the thymus in the rat was not regenerated before the intrathymic injection and the scientists used different tissue for the intrathymic injection and tissue graft. Thus, the Odorico reference is not applicable to the instant claimed method.

The Examiner has already stated that the novelty of the instant invention is the combination of the techniques. The Fahy declaration teaches the co-administration of DHEA and HGH. The Fahy declaration fails to teach intrathymic injection and organ transplant/tissue graft. Neither the instant specification nor the Fahy declaration teach

the instant invention. The prior art establishes that regeneration of age-involuted thymus and intrathymic injection has only been executed in rats. The prior art establishes the incidence of hepatic tumors, and the unpredictability regarding improvement of cellular immune function upon administration of growth hormone for thymic regeneration. Immunosuppressants are necessary for any type of organ transplant or tissue graft. Perico *et al.* disclosed that cyclosporin (CsA) and steroids used to inhibit T cell activation and to deplete them from peripheral circulation also induce changes in the structure and function of the thymus, which included a decrease in thymus epithelial and cortical cells. Immunosuppressants, which are needed for organ transplants and grafts, could affect the functional properties of a patient's thymus. Perico *et al.* state, "**all of these experiments do not yet allow conclusions to be made on whether the theoretical possibility of achieving donor-specific tolerance to allografts would possibly apply to human transplantations". "One can not exclude the possibility that the mechanism we and others have described only applies to the peculiar immune system of rats"** (Perico reference page 1069, last paragraph).

The Examiner is questioning whether the combination of all of three steps of the claimed method is enabled in a patient. Each procedure alone is difficult, thus there is no doubt that the instant invention which combines all three procedures would be extremely complex. The prior art of record teaches the drawbacks, side effects, difficulties, etc. of each step. The Examiner maintains that a large quantity of experimentation would be necessary to execute the combination of all three procedures: regenerate an involuted thymus, then administer an intrathymic injection and then

transplant an organ or tissue in a patient. The specification lacks direction and guidance for this invention. There is an absence of working examples directed to the invention.

Appellant concludes this section by stating that the claims are enabled by Appellant's specification in view of the prior art, and that the claims are definite to meet the requirement of 35 U.S.C. 112. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Respectfully submitted,

Regina M. DeBerry
October 18, 2004

Conferees
Brenda Brumback
SPE, Art Unit 1646/1647

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Gary Kunz
SPE, Art Unit 1642

BRUCE KISLIUK, DIRECTOR
TECHNOLOGY CENTER 1600

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600